



(19)

Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11)

EP 1 138 662 A1

(12)

## EUROPEAN PATENT APPLICATION

(43) Date of publication:  
04.10.2001 Bulletin 2001/40

(51) Int Cl.7: C07C 45/46, C07C 49/76

(21) Application number: 00302736.4

(22) Date of filing: 31.03.2000

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**  
Designated Extension States:  
**AL LT LV MK RO SI**

(71) Applicant: **Council of Scientific and Industrial Research**  
New Delhi 110 001 (IN)

(72) Inventors:  
• **Choudary, Boyapati Manoranjan**  
Hyderabad 500 007 (IN)

- **Sateesh, Mutyala**  
Hyderabad 500 007 (IN)
- **Kantam, Mannepalli Lakshmi**  
Hyderabad 500 007 (IN)
- **Ranganath, Kulluri Venkata Sri**  
Hyderabad 500 007 (IN)
- **Raghavan, Kondapuram Vijaya**  
Hyderabad 500 007 (IN)

(74) Representative: **Carpmael, John William Maurice**  
**CARPMAELS & RANSFORD**  
43 Bloomsbury Square  
London, WC1A 2RA (GB)

### (54) A process for the preparation of 4'-isobutylacetophenone

(57) The present invention relates to a process for the preparation of 4'-isobutylacetophenone from isobutylbenzene which comprises reacting isobutyl benzene with acetic anhydride as an acylating agent in the

presence of a zeolite beta catalyst at a temperature ranges between 60 to 165° C for 2-24 h separating the catalyst by filtration from the reaction mixture and recovering the product by a conventional method.

**Description****Field of the invention**

5 [0001] The present invention relates to a process for 4'-isobutylacetophenone (4-IBAP) by Friedel-Crafts acylation of isobutylbenzene. More particularly, this invention relates to a process for the preparation of 4'-isobutylacetophenone (4-IBAP) from isobutylbenzene using acetic anhydride as an acylating agent in the presence of nanocrystalline, micro-crystalline and metal exchanged zeolite beta catalysts.

**10 Background of the invention**

[0002] 4'-isobutylacetophenone (4-IBAP) is an important intermediate for 2-(4-isobutylphenyl)propionic acid (trade name; ibuprofen), a well-known nonsteroidal anti-inflammatory, antipyretic and analgesic drug and also other medical drugs,

15 [0003] This invention particularly relates to an ecofriendly process for 4'-isobutylacetophenone (4-IBAP) from isobutylbenzene using acetic anhydride as an acylating agent and zeolite beta as catalyst dispensing the use of stoichiometric amounts of corrosive, toxic aluminium chloride and hydrogen fluoride as Friedel-Crafts reagents.

**Prior Art References**

20 [0004] Reference may be made to a publication by Baddley et al., Journal of Chemical Society, 1956, 4943, wherein 4'-isobutylacetophenone is prepared by the Friedel-Crafts acetylation of isobutylbenzene with acetyl chloride using aluminium chloride as catalyst. Reference may be made to a US patent 3,385,886 wherein the production of ibuprofen, the first step of the process is preparation of 4'-isobutylacetophenone by the Friedel-Crafts acetylation of isobutylbenzene with acetyl chloride in the presence of aluminium of anhydrous aluminium chloride, an hazardous material that leaves large amount of solid wastes after the reaction and tedious separation process from the alumina gel to obtain the product.

25 [0005] Reference may be made to a Japanese patent publication (Early disclosure) No. 60[1985]-188,343, wherein 4'-isobutylacetophenone is prepared by the acetylation of isobutylbenzene using acetyl fluoride as an acetylating agent, prepared by reacting acetic anhydride with hydrogen fluoride as a catalyst, a combination of hydrogen fluoride and boron trifluoride. Reference may be made to US patents 4,981,995 and 5,068,448 wherein the production of ibuprofen, 4'-isobutylacetophenone is prepared by the Friedel-Crafts acetylation of isobutylbenzene with acetic anhydride using hydrogen fluoride. The 4'-isobutylacetophenone is an intermediate in a process for the production of ibuprofen. The draw-backs in the above processes are hydrogen fluoride is extremely toxic, corrosive, generation of large amount of solid wastes after the reaction and need for industrially expensive equipment to work with hydrofluoric acid.

30 [0006] The inherent disadvantages in the use of conventional Lewis acid metal chlorides for Friedel-Crafts acylation are that they are non-regenerable and require more than stoichiometric amounts because of complexation with the carbonyl product formed. Work-up to decompose the resultant intermediate complex by hydrolysis forms a large amount of waste product and separation is lengthy and expensive.

35 [0007] Obviously, different approaches have been employed for the preparation of 4'-isobutylacetophenone. There was therefore a need for a process for the preparation of 4'-isobutylacetophenone which is simple to operate and can be carried out in a media which are not toxic and corrosive. Moreover the catalyst should be simple to separate and reusable.

**45 Objects of the Invention**

[0008] The main object of the present invention is a process for the preparation of 4'-isobutylacetophenone from isobutylbenzene which comprises reacting isobutylbenzene with acetic anhydride as an acylating agent in the presence of nanocrystalline, microcrystalline and metal exchanged zeolite beta catalysts at a temperature ranges between 60 to 165° C for 2-24h separating the catalyst by filtration from the reaction mixture and recovering the product by a conventional method which obviates the drawbacks as detailed above.

50 [0009] Another object of the present invention is the use of the nano- and microcrystalline and metal exchanged nano- and microcrystalline zeolite beta as catalysts.

55 [0010] Still another object of the present invention is the metal ions selected for the exchange of nano- and micro-crystalline zeolite beta are  $\text{Fe}^{3+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ce}^{3+}$  and  $\text{La}^{2+}$ .

[0011] Still another object of the present invention is the use of acetic anhydride as an acylating agent.

[0012] Still another object of the present invention is the use of isobutylbenzene as the reaction solvent.

[0013] Still another object of the present invention is the ratio of isobutylbenzene and acylating agent is 5:1 to 1:5.

[0014] Still another object of the present invention is the quantity of the catalyst is 10 to 50% by weight with respect to the acylating agent, acetic anhydride.

[0015] Yet another object of the present invention is the reaction is effected at a temperature in the range of 60 to 165° C for 2-12h.

### 5 Summary of the Invention

[0016] The novelty of the present invention lies in the use of nanocrystalline and microcrystalline and metal exchanged nano-and microcrystalline zeolite beta for the acylation of isobutyl benzene for the first time. Decrease in particle size of zeolite beta, enhances the density of acidic sites and surface area of zeolites, which are essential factors to increase the activity of acylation reaction. In fact the activity of these nano-and microcrystalline forms increases manifold over normal zeolites. As a result of this, the acylation of isobutyl benzene is effected successfully in reasonable yields for the first time. 4'-isobutylacetophenone is obtained by a simple process involving filtration of the catalyst from the reaction mixture and recovering the product by conventional methods.

### 10 15 Detailed Description of the Invention

[0017] Accordingly, the present invention provides a process for the preparation of 4'-isobutylacetophenone, an important intermediate for ibuprofen, a widely used nonsteroidal anti-inflammatory drug wherein the said process comprises reacting isobutylbenzene with acetic anhydride as an acylating agent in the presence of nanocrystalline, microcrystalline and metal exchanged zeolite beta catalysts at a temperature ranges between 60 to 165° C for 2-24h separating the catalyst by filtration from the reaction mixture and recovering the product by a conventional method.

[0018] In an embodiment of the present invention metal exchanged, nanocrystalline and microcrystalline zeolite beta are used as the catalysts.

[0019] In an embodiment of the present invention the particle size of nanocrystalline and microcrystalline zeolite beta are 10nm to 100nm and 1μm to 50 μm.

[0020] In another embodiment of the present invention the metal ions selected for the exchange of nano- and microcrystalline zeolite beta are Fe<sup>3+</sup>, Zn<sup>2+</sup>, Ce<sup>3+</sup> and La<sup>2+</sup>.

[0021] In yet another embodiment of the present invention acetic anhydride is used as an acylating agent.

[0022] In still another embodiment of the present invention the reaction is effected at a temperature in the range of 60 to 165° C for 2-12h.

[0023] In still another embodiment of the present invention the catalyst is separated by filtration from the reaction mixture.

### 35 Scientific Explanation:

[0024] In the nano- and microcrystalline zeolite beta the density of the acidic sites increases because of increased number of broken edges resulted from the broken aluminium silicate rings. The surface area of these particles is also increased due to reduction of the particle size of zeolites. The higher density of acidic sites eventually increases number of acyl cations generated in the reaction in the electrophilic substitution of the Friedel-Crafts acylation and thus enhances activity of the reaction. Thus the higher density of acid sites present in nano-, microcrystalline, metal exchanged zeolite beta are responsible for the Friedel Crafts acylation of isobutyl benzene for the first time.

[0025] Nanocrystalline, microcrystalline and metal exchanged zeolite beta were prepared as described in example 1 and employed them in the acylation of isobutylbenzene with acetic anhydride as an acylating agent as described in examples.

[0026] The following examples are given by way of illustration of the present invention and therefore should not be construed to limit the scope of the invention.

### 40 45 Example 1

#### 50 Catalyst Preparation

##### a) Zeolite beta

[0027] Tetraethyl orthosilicate and aluminium nitrate of appropriate molar ratios to get desired ratio of Si /Al ranging from 5 to 100 were used. Water is added to tetraethylortho silicate and stirred. To this solution aluminium nitrate, nonahydrate in tetraethylammonium hydroxide solution is added dropwise by a pressure regulating funnel under stirring. After the addition, the solution is kept at 50 °C and later on kept at 135° C in an autoclave for one week for

crystallization . Then the solid was filtered and air dried. The resultant solid was calcined at 500 °C.

b) Microcrystalline zeolite beta-I

5 [0028] Microcrystalline zeolite beta-I was obtained by mechanical disintegration of the zeolite beta obtained as described above (1 $\mu$ m -10 $\mu$ m, 95%).

c) Microcrystalline zeolite beta-II

10 [0029] Microcrystalline zeolite beta was synthesised with different particle size (5 $\mu$ m to 50  $\mu$ m, 85%) by decreasing ageing time to 48 hours instead of one week during the synthesis of zeolite beta according to the above procedure.

d) Nanocrystalline zeolite beta

15 [0030] Nanocrystalline zeolite beta was synthesised with different particle size (10 nm to 100 nm) from the homogenised solution prepared in the first step of zeolite beta which is kept for crystallisation at different times by decreasing aging time to control the nucleation growth of zeolite during the synthesis. Then the solid were separated by centrifugation and resultant solid was washed with distilled water and dried at 100 °C.

20 e) Metal exchanged zeolite beta

[0031] 10 g of zeolite beta as synthesised or microcrystalline zeolite beta having Si/Al= 15 was subjected to an ion-exchange procedure by stirring with 1wt% to 10wt% metal chloride ( $Ce^{3+}$ ,  $Fe^{3+}$ ,  $Zn^{2+}$  and  $La^{2+}$ ) solution at 80 °C for 6 hours. The resultant zoolite was washed with deionised water and dried at 120 °C. After that the metal exchanged zeolite was calcined at 500 °C for 6 hours.

f) H<sup>+</sup>-exchanged zeolite beta

30 [0032] Zeolite beta is added to 1 Molar  $NH_4Cl$  solution (10ml/g zeolite), stirred at 60°C for 6 hours and the resultant solid was washed with deionised water and dried at 120° C. After that ammonium exchanged zeolite was calcined at 500 °C to get H<sup>+</sup>-exchanged zeolite beta.

**Example 2**

35 [0033] A mixture of isobutylbenzene (40 mmol), acetic anhydride (10 mmol) and zeolite beta catalyst ( 0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 0.11 g

40 **Example 3**

[0034] A mixture of isobutylbenzene (1.5mol) acetic anhydride (0.375mol) and microcrystalline zeolite beta-I catalyst (20 g) were stirred in a round bottomed flask (1 lit) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 13.4 g

**Example 4**

50 [0035] A mixture of isobutylbenzene (40 mmol), acetic anhydride (10 mmol) and microcrystalline zeolite beta-II catalyst (0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 0.42 g

55 **Example 5**

[0036] A mixture of isobutylbenzene (40mmol) acetic anhydride (10 mmol) and H<sup>+</sup>-exchanged microcrystalline zeolite beta-I catalyst (0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture

to obtain the crude product. Yield: 0.36 g

#### Example 6

[0037] A mixture of isobutylbenzene (40mmol) acetic anhydride (10 mmol) and Fe<sup>3+</sup>-exchanged zeolite beta catalyst (0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 0.21 g.

#### Example 7

[0038] A mixture of isobutylbenzene (40mmol), acetic anhydride (10 mmol) and La<sup>3+</sup>-exchanged zeolite beta catalyst (0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 0.26 g

#### Example 8

[0039] A mixture of isobutylbenzene (40mmol), acetic anhydride (10 mmol) and Ce<sup>3+</sup>-exchanged microcrystalline zeolite beta-II catalyst (0.5 g) were stirred in a round bottomed flask (50 ml) under nitrogen atmosphere at 130 °C temperature. After completion of the reaction (followed by G. C.), the reaction mixture was filtered and distilled the reaction mixture to obtain the crude product. Yield: 0.52 g.

Table 1

Acylation of isobutyl benzene with acetic anhydride by various zeolite beta catalysts.			
Example No.	Catalyst	Time (h)	Isolated yield (%)
2	Zeolite beta	8	6
3	Microcrystalline beta-I	6	20
4	Microcrystalline beta-II	3	25
5	H <sup>+</sup> microcrystalline beta-I	6	20
6	Fe <sup>3+</sup> -beta	8	12
7	La <sup>3+</sup> -beta	6	15
8	Ce <sup>3+</sup> -micro crystalline beta-II	3	30

[0040] The main advantages of the present invention are:

1. A novel and ecofriendly process for the preparation of 4'-isobutylacetophenone.
2. The present process eliminates the use of corrosive and stoichiometric quantities of aluminium chloride.
3. Nanocrystalline, microcrystalline and metal exchanged zeolite beta have been used as catalysts for the acylation of Isobutylbenzene for the first time.
4. Work-up procedure is simple.
5. The present process envisages no disposal problem as the catalyst can be used for several cycles. The catalyst was subjected to 4 recycles which displayed consistent activity.
6. The present process is environmentally safe since there is no disposal problem.
7. The process is economical.

#### Claims

1. A process for the preparation of 4'-isobutylacetophenone from isobutylbenzene which comprises reacting isobutyl benzene with acetic anhydride as an acylating agent in the presence of a zeolite beta catalyst at a temperature ranges between 60 to 165° C for 2-24h separating the catalyst by filtration from the reaction mixture and recovering the product by a conventional method.

2. A process as claimed in claim 1 wherein the zeolite beta catalyst is selected from nano crystalline, microcrystalline and metal exchanged zeolite beta.
- 5 3. A process as claimed in claim 1 wherein the particle size of nanocrystalline and microcrystalline zeolite beta are 10 nm to 100 nm and 1 $\mu$ m to 50  $\mu$ m
- 10 4. A process as claimed in claim 1 wherein metal ions selected for exchange are Ce<sup>3+</sup>, Zn<sup>2+</sup>, Fe<sup>3+</sup>, and La<sup>2+</sup>
5. A process as claimed in claim 1 wherein acetic anhydride is used as an acylating agent.
- 10 6. A process as claimed in claim 1 wherein the reaction is effected at a temperature in the range of 60 to 165° C for 2-12 hrs.

15

20

25

30

35

40

45

50

55



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 00 30 2736

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)						
X	EP 0 701 987 A (UETIKON CHEMIE AG) 20 March 1996 (1996-03-20) * the whole document *	1,5,6	C07C45/46 C07C49/76						
X	WO 97 48665 A (RHONE-POULENC CHIMIE) 24 December 1997 (1997-12-24) * claims 1,24; example 8 *	1,5,6							
X	DATABASE WPI Section Ch, Week 199522 Derwent Publications Ltd., London, GB; Class B05, AN 1995-167205 XP002149028 & JP 07 089893 A (TORAY IND INC). 4 April 1995 (1995-04-04) * abstract *	1							
-----									
TECHNICAL FIELDS SEARCHED (Int.Cl.)									
C07C									
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>3 October 2000</td> <td>Bonnevalle, E</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	3 October 2000	Bonnevalle, E
Place of search	Date of completion of the search	Examiner							
THE HAGUE	3 October 2000	Bonnevalle, E							
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone      Y : particularly relevant if combined with another document of the same category      A : technological background      O : non-written disclosure      P : intermediate document</p> <p>T : theory or principle underlying the invention      E : earlier patent document, but published on, or after the filing date      D : document cited in the application      L : document cited for other reasons      S : member of the same patent family, corresponding document</p>									

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 00 30 2736

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

03-10-2000

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0701987	A	20-03-1996	JP	8176058 A	09-07-1996
WO 9748665	A	24-12-1997	FR	2750132 A	26-12-1997
			AU	3347997 A	07-01-1998
			BR	9709734 A	10-08-1999
			EP	0906254 A	07-04-1999
			NO	985912 A	22-02-1999
			ZA	9705413 A	25-08-1998
JP 7089893	A	04-04-1995		NONE	